Steroidal Sapogenins. LII. Structure and Properties of the Acetyl Hypobromite Adduct from a Δ^{16}-Pregnen-20-one[2a,b]

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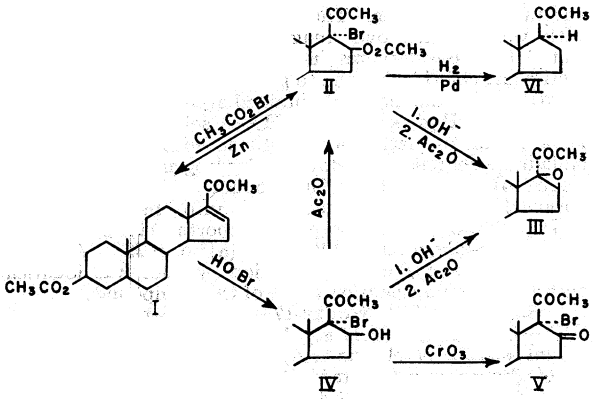
The adduct from acetyl hypobromite and 3β-acetoxy-5α-pregn-16-en-20-one is shown to be 3β,16β-diacetoxy-17α-bromo-5α-pregnan-20-one. The marked resistance of this compound toward C_{21}-bromination is described and the possible utility of this property is indicated.

The addition of acetyl hypobromite to 3β-acetoxy-5α-pregn-16-en-20-one (I) to give a bromohydrin acetate was described in the previous communication.[2] Since the double bond involved in this facile reaction is part of a conjugated ketone system,[3] we felt unjustified in adducing, in this case, the same mechanistic principles[2] which aided in our assignment of structures to the adducts from isolated double bonds.[4] This paper records the evidence on which the 16β-acetoxy-17α-bromo structure (II) was assigned to this addition product.

When II was treated with zinc dust or with Raney nickel, the conjugated ketone I was regenerated, indicating that the acetyl hypobromite addition was accompanied by no gross structural change. Saponification of II, followed by mild acetylation produced an epoxyketone formulated as 3β-acetoxy-16β,17β-epoxy-17-iso-5α-pregnan-20-one (III), since it was not identical with the known, corresponding α-oxide.[5] The two oxides are also known in the Δ^5-series[6] and, in both series, the molecular rotation of the β-oxide is the more positive by 400 ± 35°.[7] Since these data are consistent with a 16α-bromo-17β-acetoxy structure as well as with II, additional structure evidence was required.

Treatment of I with N-bromoacetamide under the usual[8] conditions of hypobromous acid addition gave a halohydrin (IV) which, on acid-catalyzed acetylation, produced II in high yield. The structural correspondence between these two compounds was also manifested in the ready conversion of IV to the same β-oxide (III) as was obtained from II.



The position of attachment of the new oxygen function in these adducts could now be ascertained. Chromic acid oxidation of the bromohydrin IV yielded a bromodione-3-acetate V showing no hydroxyl absorption in the infrared but possessing a new carbonyl band at 1742 cm.$^{-1}$ (5-ring ketone[9]). This establishes the secondary (16β)-alcohol structure IV for the bromohydrin[10] and, consequently, fixes II as the structure of the acetyl hypobromite adduct.

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture, Article not copyrighted.

(2) (a) Presented in part at the 135th National A.C.S. Meeting, Boston, Mass., April 5–10, 1959; (b) paper LI, S. G. Levine and M. E. Wall, This Journal, **81**, 2826 (1959).

(3) Reaction of the same reagent with another conjugated ketone, progesterone, resulted in the formation of an intensely colored, intractable product mixture from which only a small amount of starting material could be recovered. *Cf.* the addition of hypobromous acid to the conjugated double bond of cortisone acetate [E. P. Oliveto, C. Gerold and E. B. Hershberg, *ibid.*, **79**, 3596 (1957)].

(4) In particular, a mechanism based on initial electrophilic attack by "Br^{+}" from the less hindered (α) side of the molecule may not be operative with Δ^{16}-20-ketones which have been shown to be particularly labile toward nucleophilic addition [*E.g.*, see D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951)].

(5) Pl. A. Plattner, L. Ruzicka, N. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 385 (1947).

(6) B. Löcken, S. Kaufmann, G. Rosenkranz and F. Sondheimer, This Journal, **78**, 1738 (1956).

(7) Physical properties of 3β-acetoxy-16,17-epoxy-pregnan-20-ones:

		M.p., °C.	[M]D	Ref.
5αH	16β,17β	157–159	−240°	Present study
	16α,17α	186–187	+193°	5
Δ^5	16β,17β	176–178	−402°	6
	16α,17α	156–158	− 37.2°	6

(8) See paper cited in ref. 3.

(9) The unshifted position of this absorption band is not surprising in view of the quasi-axial orientation of the 17α-bromine atom. The failure of this substituent to exert a hypsochromic effect on 20-ketone absorption is also illustrated in V, $\bar{\nu}_{max}$ 1710 cm.$^{-1}$, as well as in II, $\bar{\nu}_{max}$ 1705 cm.$^{-1}$, and has already been commented on by R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, This Journal, **74**, 2828 (1952).

(10) Sondheimer, *et al.* (ref. 6), have prepared the corresponding bromohydrin in the Δ^5-pregnene series to which these authors assign an identical ring D structure based on a different line of evidence. It may be noted that their bromohydrin was apparently stable toward zinc reduction whereas the similar bromohydrin *acetate* II is converted, under these conditions, to the conjugated ketone I. Also, palladium hydrogenation of their bromohydrin yielded a 16β-hydroxy-20-ketone in contrast to the ring D unsubstituted 20-ketone obtained by hydrogenation of II.

It is interesting to note that II was recovered unchanged after subjection to various bromination conditions. Thus this compound survived treatment with bromine in glacial acetic acid or in chloroform, both reaction solutions containing hydrobromic acid as catalyst. Similar results were obtained when bromination under homolytic conditions was attempted.

Thus, the C_{21}-methyl group is, in some way, effectively "protected" against bromination by the 16β-acetoxy-17α-bromo combination. We have already described[2b] the resistance of acetyl hypobromite adducts toward other common reaction conditions and also their ease of reductive reversion to the parent olefin. These properties have lent themselves to a variety of synthetic applications which are now being investigated and will be reported subsequently.

Experimental[11]

Reduction of II to 3β-Acetoxy-5α-pregn-16-en-20-one (I). (a) Using Raney Nickel.—Thirty mg. of II[2] was treated with 0.47 g. of Raney nickel using the procedure of Barkley, *et al.*[12] The product was crystallized from hexane as blades (17.5 mg., 81%) MeOH λ_{max} 239, log ϵ 3.95, m.p. 162–165°, not depressed by admixture with an authentic sample.

(b) Using Zinc Dust.—Ninety-nine mg. of II, 1.0 g. of zinc dust and 10 ml. of ethanol were heated under reflux with stirring for 3 hours. The mixture was filtered, concentrated, and taken up in ether. The ether solution was then washed with water, dried over magnesium sulfate, and concentrated to a powdery residue which was crystallized from methylene chloride–hexane to give 50 mg. (70%) of product identical with the material obtained above.

Palladium Hydrogenation of II.—A solution of 0.249 g. of II in 15 ml. of methanol was stirred with 0.125 g. of 5% palladium–charcoal. Uptake of hydrogen (2 equivalents) ceased after 20 minutes. The product, 0.126 g. (70%), was obtained as plates from methanol, m.p. 142–143°, $[\alpha]^{25}D$ + 78°, no ultraviolet absorption; reported[13] for 3β-acetoxy-5α-pregnan-20-one, m.p. 140–141°, $[\alpha]^{22}D$ + 72°. An infrared spectrum of the hydrogenation product was identical with that of an authentic sample of this compound.

3β-Acetoxy-16β-hydroxy-17α-bromo-5α-pregnan-20-one (IV).—Compound I (2.17 g.), 1.70 g. of N-bromoacetamide, 2.0 ml. of 72% perchloric acid, 20 ml. of water and 200 ml. of tetrahydrofuran (treated with, and distilled from sodium hydroxide) were mixed at 4° and allowed to remain at that temperature for 24 hours. The reaction mixture was then neutralized with potassium acetate, concentrated to about one-third original volume, diluted with cold water, and extracted with methylene chloride. The organic solution was thoroughly washed with water, dried over sodium sulfate, and concentrated almost to dryness. The residue was then crystallized from aqueous methanol yielding 1.50 g. (54%) of prisms, m.p. 173–177°. Three recrystallizations from hexane gave a sample, m.p. 175–177°, $[\alpha]D$ + 6.8°. The infrared spectrum had bands at 3480 (strong, H-bonded 16-OH), 1730 (acetate), 1690 (20-ketone, H-bonded), 775 (Br); there was no high-intensity absorption in the ultraviolet. *Anal.* Calcd. for $C_{23}H_{35}O_4Br$: C, 60.66; H, 7.75, Br, 17.55. Found: C, 60.54; H, 8.03; Br, 17.78. An aliquot withdrawn after 5.5 hours and worked-up similarly had λ_{max}^{MeOH} 239, ϵ 2,000.

Conversion of IV to III.—In a manner similar to the conversion[2] of 17α-bromo-3β,16β-diacetoxy-5α-pregnan-20-one to the epoxide III, saponification and acetylation of 0.500 g. of the bromohydrin IV yielded 0.27 g. (70%) of the β-oxide III, m.p. 158–159°, not depressed by admixture with a sample prepared from the acetyl hypobromite adduct. The infrared spectra of the two samples were identical.

17α-Bromo-3β,16β-diacetoxy-5α-pregnan-20-one from IV.—Compound II (50 mg.) was dissolved in 1.0 ml. of glacial acetic acid containing 0.2 ml. of acetic anhydride and 10 mg. of *p*-toluenesulfonic acid and kept at 25° for 24 hours. After addition of 10 ml. of cold water the product was collected, washed with water, dried, and recrystallized from methylene chloride–methanol yielding 33 mg. (61%) of II, m.p. 209–215°[14] alone or admixed with a sample of II prepared from I and acetyl hypobromite. The infrared spectra of the two samples were identical.

3β-Acetoxy-17α-bromo-5α-pregnan-16,20-dione (V).—A solution of 0.700 g. of chromic oxide in 1 ml. of water was added over 20 minutes to a cooled (10°) solution of 0.700 g. of the bromohydrin IV in 2 ml. of methylene chloride and 15 ml. of acetic acid. After one hour at 20° the reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was then washed with cold, dilute sodium bisulfite and then repeatedly with cold water. The product (0.392 g., 56%) was obtained by crystallization from methanol m.p. 164–167°, $[\alpha]^{25}D$ −48.3°. The infrared spectrum had bands at 1742 (16-ketone), 1732 (acetate), 1705 (20-ketone). *Anal.* Calcd. for $C_{23}H_{33}O_4Br$: C, 60.92; H, 7.34; Br, 17.64. Found: C, 61.06; H, 7.33; Br, 17.78.

Treatment of II with Potassium Acetate.—Compound II (0.10 g.) was heated under reflux with 0.10 g. of potassium acetate in 15 ml. of dry acetone for 3 hours; 0.3 g. additional potassium acetate was added and heating continued for 2 hours longer. Solvent was evaporated and the residue taken up in ether and washed with water. From the dried, concentrated ether solution was obtained 0.08 g. of II, identical with starting material in melting point, mixture melting point and infrared spectrum.

Treatment of II with Potassium Iodide.—A similar experiment was carried out with 50 mg. of II and 50 mg. of potassium iodide in 15 ml. of acetone. Starting material was recovered in 90% yield on the same basis as above.

Attempted Bromination of II. (a) Ionic Conditions.—A solution of 1.15 g. of II and 370 mg. of bromine in 25 ml. of chloroform containing 0.1 ml. of 5 *N* hydrogen bromide in acetic acid was allowed to remain at 25° for 24 hours. No bromine uptake could be detected by thiosulfate titration of an aliquot. Treatment of the resulting solution with cold, dilute, sodium bisulfite followed by washing and drying led to the recovery of 0.920 g. of starting material.

(b) Free Radical Conditions.—A solution of 0.25 g. of II, 0.089 g. of N-bromosuccinimide and 16 mg. of azodiisobutyronitrile[15] in 30 ml. of benzene was heated under reflux in a nitrogen atmosphere for 3 hours. The solution was then cooled and washed with water. Crystallization from methanol then yielded 80 mg. of starting material. A similar experiment using dibenzoyl peroxide as catalyst in refluxing carbon tetrachloride solution gave similar results. When the latter reaction was repeated in a quartz vessel and with ultraviolet irradiation, reduction of the reagent to succinimide took place, together with the formation of a small amount of resinous, enolic material and 90% of II was recovered unchanged.

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(11) Infrared spectra were obtained in carbon disulfide solution, 10.0 g./liter. Optical rotations were measured in chloroform solution using a 2-decimeter tube, approximately 12.5 g./liter. We wish to thank C. S. Fenske and C. T. Leander for infrared data, S. Serota for optical rotations and Ruth B. Kelly for elemental analyses. Specification of brand names of materials used does not imply endorsement over similar commercial products.

(12) L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, THIS JOURNAL, **76**, 5017 (1954).

(13) J. Y. F. Paterson and W. Klyne, *Biochem. J.*, **42**, ii (1948).

(14) Compound II displayed a variable melting point depending on the rate of heating. Melting was accompanied by slight browning indicative of partial decomposition.

(15) C. G. Overberger, *et al.*, THIS JOURNAL, **71**, 2661 (1949).